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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,844	02/03/2006	Tatsuo Hoshino	21425 US C038435/0185658	2034

7590 10/12/2007

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,844	HOSHINO ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

In response to a previous Office action, a non-final action (mailed on April 18, 2007), Applicants filed a response and amendment received on July 23, 2007, amending claims 1-3 is acknowledged. Claims 1-3 are pending in the instant Office action.

Thus, claims 1-3 will be examined herein.

Applicants' arguments filed on April 18, 2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgement is made of applicants claim for foreign priority of EP 02021641.2 of 9/27/2002. The priority date of EP has been granted as foreign priority EP is an English language document and has the support of the instant application.

Maintained-Claim Rejections - 35 USC § 112(2nd)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Previous rejection of Claims 1-3 under 35 U.S.C. 112, second paragraph, as being indefinite and vague in the recitation "stringent hybridization and stringent washing conditions" is maintained.

Applicants argue that the hybridization and wash conditions are clearly disclosed at, *e.g.*, page 3, lines 15-21 of the specification and based on this disclosure and with a view towards

furthering prosecution, claim 1 has been amended to recite "stringent hybridization and stringent washing conditions."

This is not found persuasive because claim 1 still reads on conditions that are not clearly defined, although page 3 describe a condition, the description is merely exemplary. In the art the meaning of the term "standard" varies widely depending on the individual situation and the person making the determination. Therefore, the rejection is maintained.

Maintained - Claim Rejections - 35 U.S.C. § 112(1st)

Previous rejection of Claims 1-3 under 35 U.S.C. 112, first paragraph, enablement requirement, is maintained. This rejection has been described at length in previous Office Action. The rejection is maintained for the following reasons.

Applicants argue that it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling and the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention.

Applicant's amendment to claims and arguments fully considered but are not to be persuasive to overcome the rejection on enablement issues. Claim 1 (part (d)) still reads on any DNA sequence which is 80% identical to SEQ ID NO: 1 or any DNA sequence encoding a polypeptide which is 80% identical to SEQ ID NO: 2, which is 20% non-identical i.e. 99 amino acid residues are different out of 496 amino acid protein, that includes many mutants and variants. Applicants are silent about this issue. The Examiner clearly established the enablement

rejection in the previous Office action and the applicants addressed some of the issues by amending claims and arguments.

As mentioned in the previous Office Actions, the specification, while being enabling for a process for the biological production of vitamin B6 comprising cultivating a Sinorhizobium cell transformed or transfected by a DNA molecule of SEQ ID NO: 1 from S. meliloti encoding a polypeptide of SEQ ID NO: 2 having D-erythronate-4-phosphate dehydrogenase activity, does not reasonably provide enablement for a process for the biological production of vitamin B6 comprising cultivating a Sinorhizobium or Escherichia host cell transformed or transfected by any DNA molecule encoding any polypeptide, which is 80% identical to SEQ ID NO: 1 or SEQ ID NO: 2 having flavin adenine dinucleotide-dependent D-erythronate 4-phosphate dehydrogenase activity.

The scope of the claimed invention is very broad in the context of at least 80% identity to SEQ ID NO: 1 or 2. How many polypeptides having D-erythronate-4-phosphate dehydrogenase activity can be encompassed by these claims? The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as D-erythronate 4-phosphate dehydrogenase requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this

would clearly constitute **undue** experimentation. Guo et al. (Protein tolerance to random amino acid change, Proc Natl Acad Sci U S A, 2004 Jun 22; 101(25): 9205-10, Epub 2004 Jun 14) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant protein 80% identity allows up to 99 mutations within the 496 amino acids of SEQ ID NO: 2 and thus only $(.66)^{99}$ X 100% or 1.3 x 10^{-16}% (i.e. $\cong$ 1 in several billion) of random mutants having 80% identity would be active. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within many billions or more as in the claims to 80% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Sufficient guidance has **not** been provided in the instant specification or in the prior art as at best art teaches to avoid changes of 20% of the structure of SEQ ID NO: 2 but does little to suggest what changes would be successful particularly for those enzymes having the substantial number of alterations necessary to produce a protein having 80% identity to SEQ ID NO: 2.

Withdrawn-Claim Rejections - 35 USC § 103

Previous rejection of Claims 1-2 under 35 U.S.C. 103 (a) as being obvious over Capela et al. (GenBank Accession No. AL591783 for nucleic acid, created 8/1/2001, and GenBank Accession No. Q92SG4, for protein, created 12/1/2001), Capela et al. (Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain 1021, Proc Natl Acad Sci U S A. 2001 Aug 14; 98(17): 9877-82. Epub 2001 Jul 31, see IDS) in view of Yocum et al. (US PGPUB 2005/0164335 A1, publication 7/28/2005, claim priority of 60/367,863 of 3/25/2002 and 60/368,618 of 3/29/2002) is withdrawn in view of applicants amendment of claims and persuasive arguments. Since, Capela et al. (UniProt) teach a protein sequence based on genome sequence of S. meliloti predicted to be a putative oxidoreductase type protein, one of one of skilled artisan would not be expected to use the encoding oxidoreductase protein of Capela et al. to combine with the method of producing vitamin B6 as taught by Yocum et al. at the time of invention was made to produce vitamin b6 by using said oxidoreductase gene. The sequence identity data also suggest that there were no sequence having significant sequence identity to SEQ ID NO: 2 to suggest or motivate to use oxidoreductase type of gene encoding protein could be used for vitamin B6 biosynthesis. Therefore, the rejection is withdrawn.

Similarly, previous rejection of Claim 3 under 35 U.S.C. 103 (a) as being obvious over Capela et al. (GenBank Accession No. AL591783 for nucleic acid, created 8/1/2001, and GenBank Accession No. Q92SG4, for protein, created 12/1/2001), Capela et al. (Analysis of the chromosome sequence of the legume symbiont Sinorhizobium meliloti strain 1021, Proc Natl Acad Sci U S A. 2001 Aug 14; 98(17): 9877-82. Epub 2001 Jul 31, see IDS) in view of Yocum

et al. (US PGPUB 2005/0164335 A1, publication 7/28/2005, claim priority of 60/367,863 of 3/25/2002 and 60/368,618 of 3/29/2002) and further in view of Tazoe et al. (Biosynthesis of vitamin B6 in Rhizobium: in vitro synthesis of pyridoxine from 1-deoxy-D-xylulose and 4-hydroxy-L-threonine, Biosci Biotechnol Biochem. 2002 Apr; 66(4): 934-6) is withdrawn in view of applicants amendment of claim and persuasive arguments. The reason of withdrawn is based on same explanation as discussed above.

Conclusion

No claims are allowed.

Applicants must respond to the objections/rejections in each of the sections in this Office action to be fully responsive in prosecution. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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